

# Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death

Lena Avedissian, Jennifer A. McNear, David A. Appel, Laudino M. Castillo-Rojas, J. Edwin Atwood, Lisa A. Pearse, Robert N. Potter, Allen P. Burke, Ladd Tremaine, Philip J. Gentlesk, Eric A. Shry, S. Scott Reich, Robert E. Eckart

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San Antonio, TX and Washington, DC



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# Myocarditis

- ◆ Myocarditis as a cause of sudden death in the young population has widely variable incidence, ranging from 5 to 42%.
- ◆ Men may be more predisposed than women to develop myocarditis.
- ◆ Worse outcome in the younger population.
  - ◆ 162 subjects under the age 40 with myocarditis
  - ◆ Sudden death seen in 22% of those <30 years compared to only 11% in those between 30-40 years

# Etiologies

## Infectious myocarditis

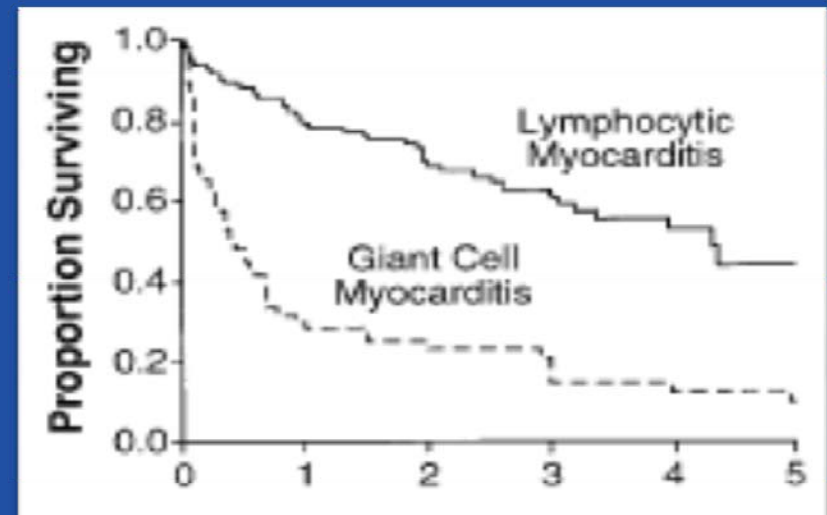
Enterovirus	Herpes virus	Rickettsial	Bacterial
Coxsackie A and B	Mumps	Fungal	Legionella
ECHO	Rubella	<i>Cryptococcus</i>	Clostridium
Influenza	Rubeola	Protozoan	Salmonella/Shigella
Polio	Hepatitis B and C	<i>Trypanosomiasis cruzi</i>	Spirochetal
Adenovirus	HIV	<i>Toxoplasmosis gondi</i>	<i>Borrelia burgdorferi</i>

## Noninfectious Myocarditis

Cardiotoxic drugs	Hypersensitivity drug reactions	
Catecholamines	Antibiotics	Diuretics
Doxorubicin	Ampicillin	HCTZ
Systemic illness	Tetracycline	Spironolactone
SLE	Sulfisoxazole	Others
Other collagen disease		Lithium
Sarcoidosis		Indomethecin

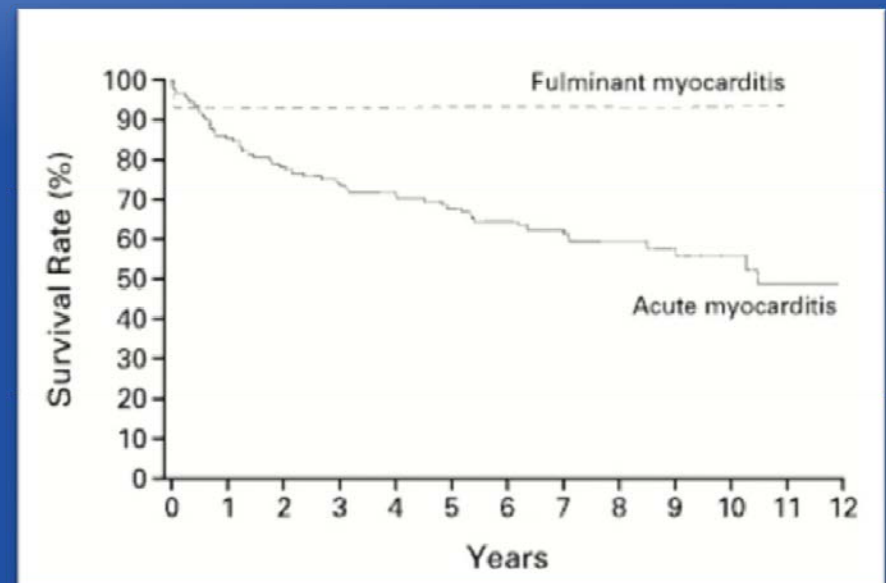
# Classifications of Myocarditis

- ◆ Active viral infection
- ◆ Postviral or lymphocytic myocarditis
- ◆ Other infectious etiologies
- ◆ Hypersensitivity myocarditis
- ◆ Giant cell myocarditis
  - ◆ Multinucleated giant cells
  - ◆ High mortality



# Clinical Presentation

- ◆ Fulminant myocarditis
  - ◆ Acute critical illness
  - ◆ Distinct viral prodrome
  - ◆ Multiple foci of active myocarditis by histology
  - ◆ Favorable prognosis
- ◆ Acute myocarditis
  - ◆ Less distinct onset
  - ◆ Hemodynamically stable
- ◆ Chronic Myocarditis
  - ◆ Manifest with heart failure secondary to dilated cardiomyopathy

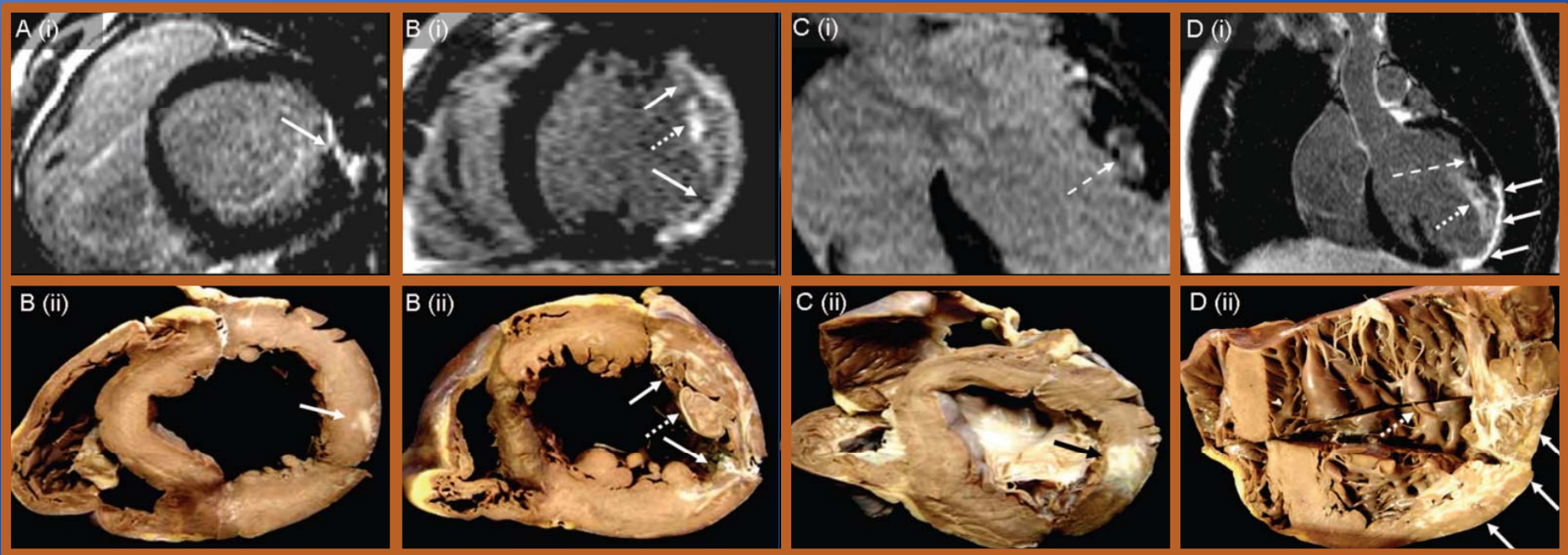


# Contributors to malignant cardiac arrhythmias in myocarditis

- ◆ Structural changes in the region of the injured myocardium, during both active myocarditis and healing (deleterious ventricular remodeling).
- ◆ Inflammatory process in the cardiac myocytes and interstitium can lead to fluctuations in the membrane potential.
- ◆ Activated neutrophils have been associated with generation of early after depolarization



# Fibrosis and scarring as substrate for both automaticity and reentry





# Study Design

- ◆ Review of non-traumatic sudden death within the Department of Defense with an available clinical record or autopsy for adjudication as to the cause of death.
- ◆ Statistical measures
  - ◆ Categorical variables were compared using the  $\chi^2$  test or the Fisher exact test and the Student's  $t$ -test was used to compare normally distributed continuous variables.
  - ◆ Differences considered statistically significant if  $p < 0.05$ .
  - ◆ JMP Professional (SAS Institute Inc., Cary, NC).
- ◆ Sponsored by the Air Force Medical Research Program (AF/SGRS).

# Defining the Cohort

- ◆ 902 non-traumatic suspected cardiac deaths
  - ◆ 1998 to 2008
  - ◆ Records available for review in which adjudicated cause of death was of cardiac etiology
- ◆ Identified 30 subjects with death due to myocarditis. Used 187 subjects with structurally normal heart as control group.

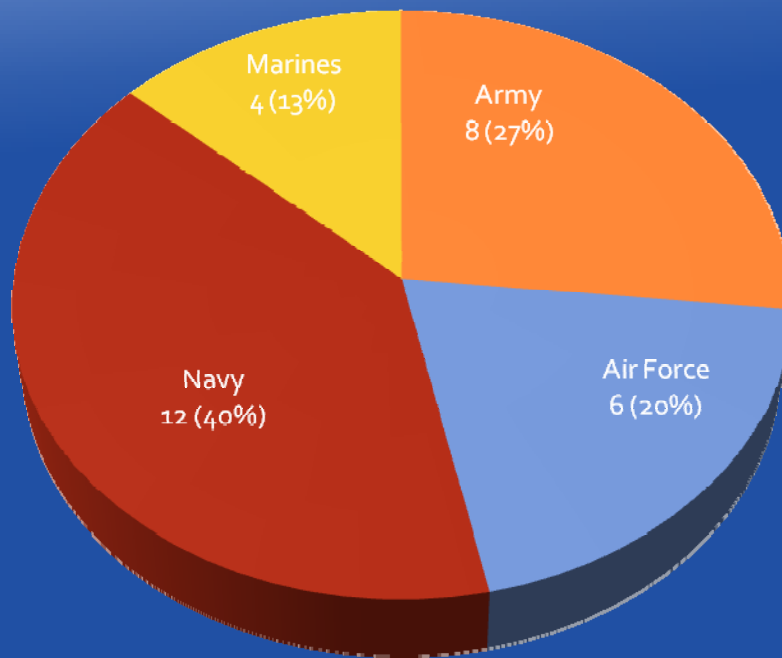
# Results

	Myocarditis n=30	Idiopathic SCD n=187	p-value
Age, years	32±10	32±11	0.940
Gender, % male	26 (86.7%)	174 (93.1%)	0.265
Prodromal symptoms	16/23 (69.6%)	48/99 (48.5%)	0.104
Fever, headache, URI symptoms	13/23 (56.5%)	0/99 (0.0%)	<0.001
Out of hospital death	5 (16.7%)	55(29.4%)	0.219

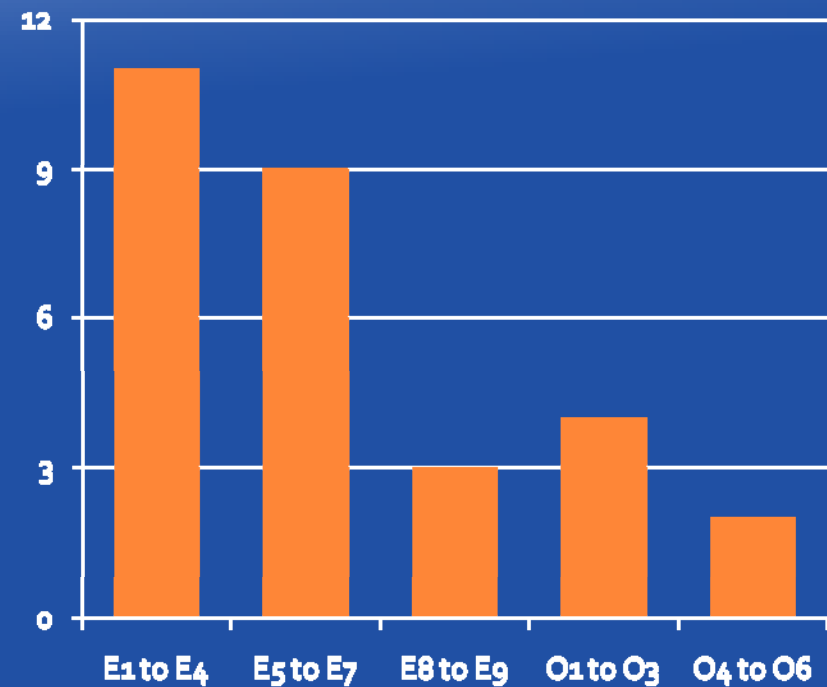
# Baseline Characteristics

Military specific findings for those with death due to myocarditis

**Branch**



**Column2**



Not shown is the 1 Warrant Officer

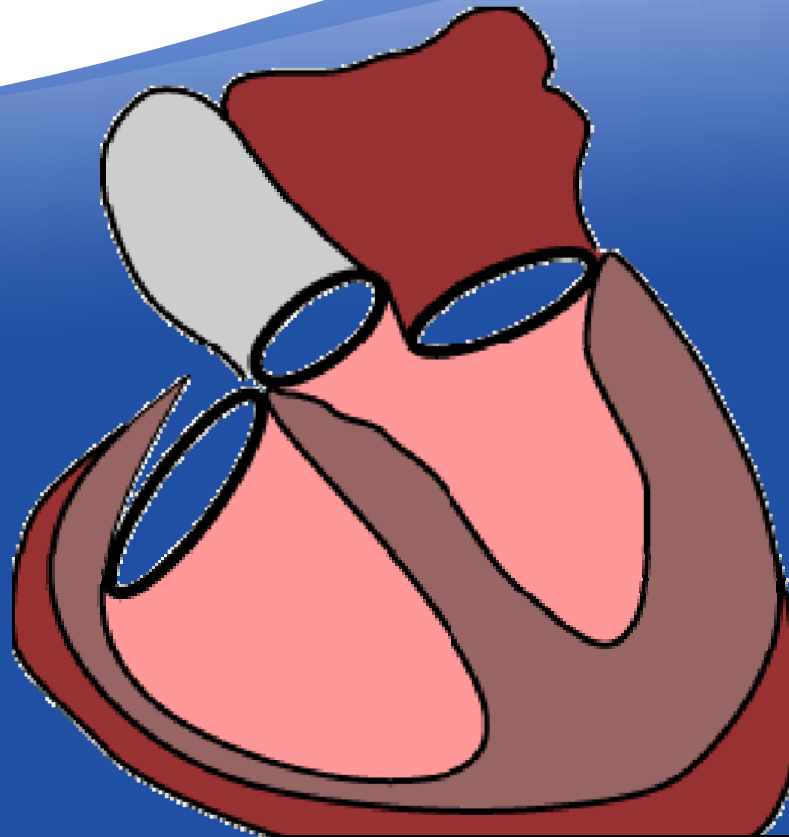
# Results

	Myocarditis n=30	Idiopathic SCD n=187	p-value
Myocardial measurements			
Cardiac mass, gms	451±88	395±72	<0.001
LV thickness, cm	1.6±0.4	1.5±0.3	0.033
RV thickness, cm	0.5±0.2	0.4±0.2	0.457
Valve circumference			
TV annulus, cm	13.7±2.0	12.7±1.7	0.158
PV annulus, cm	8.0±1.9	7.1±1.0	0.092
MV annulus, cm	11.1±1.0	10.7±1.1	0.385
AV annulus, cm	7.2±0.7	6.8±0.8	0.213
Histologic findings			
Fibrosis	11 (36.7%)	34 (18.2%)	0.038
Necrosis	13 (43.3%)	5 (2.7%)	<0.001
Disarray	2 (6.7%)	5 (2.7%)	0.250

# Ventricular specification

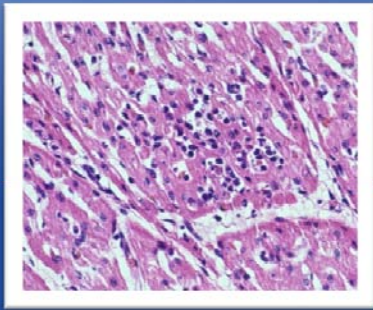
Isolated Right Ventricle  
Involvement  
31.3%

Isolated Left Ventricle  
Involvement  
25.0%

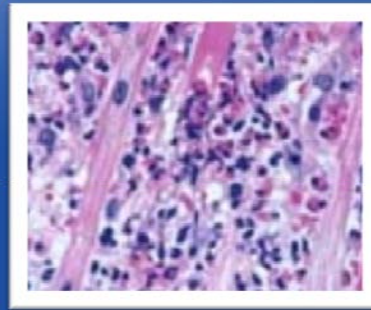


Bi-ventricle  
Involvement  
43.8%

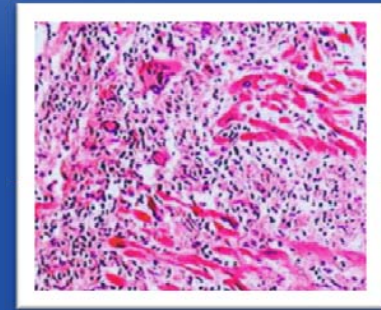
# Findings on Examination



Lymphocytic  
81.8%



Eosinophilic  
4.5%



Giant Cell  
9.1%

Findings on gross examination to suggest myocarditis were noted in 85.7% of cases.



# Conclusion

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# Defining Myocarditis

## ◆ Dallas Classification (1987)

- ◆ Myocarditis: Myocardial necrosis, degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrate with or without fibrosis.
- ◆ Borderline myocarditis: Inflammatory infiltrate too sparse or myocyte damage not apparent.
- ◆ No myocarditis:

## ◆ WHO Marburg Criteria (1996)

- ◆ Acute (active) myocarditis: A clear-cut infiltrate (diffuse, focal or confluent) of  $>14$  leukocytes/mm<sup>2</sup> (preferably activated T-cells). The amount of the infiltrate should be quantitated by immunohistochemistry. Necrosis or degeneration are compulsory, fibrosis may be absent or present and should be graded.
- ◆ Chronic myocarditis: An infiltrate of  $>14$  leukocytes/mm<sup>2</sup> (diffuse, focal or confluent, preferably activated T-cells). Quantification should be made by immunohistochemistry. Necrosis or degeneration are usually not evident, fibrosis may be absent or present and should be graded.
- ◆ No myocarditis: No infiltrating cells or  $<14$  leukocytes/mm<sup>2</sup>.